REMARKS

Claims 1-40, 42-44, and 46-65 are pending in the application. Claims 1-40, 42-44, and 46-54 have been withdrawn by the Office. Claims 41 and 45 have been canceled without prejudice or disclaimer. Claims 55-65 have been added. Support for the new claims can be found throughout the specification as originally filed, for example at original claims 41 and 45; page 20, line 8; page 45, line 23; page 47, line 10; and page 48, line 34 to page 51, line 14. The amendments add no new matter to the specification.

Telephonic Discussion

Applicants' representative thanks Examiner Steadman for speaking with him on October 1, 2009 regarding the Office Communication mailed September 8, 2009. According to the Communication, "[t]he amendment filed on 5/26/09 canceling all claims drawn to the elected invention and presenting only claims drawn to a non-elected invention is non-responsive (MPEP § 821.03)." In the telephonic discussion, the Examiner indicated that claims to methods comprising contacting a nucleic acid encoding an anergy associated E3 ubiquitin ligase in a cell with either an antisense nucleic acid or a small interfering RNA molecule might be includible in applicants' elected restriction group, but since no nucleic acid sequences have been searched, a Request for Continued Examination should be filed if applicants wish to pursue those claims. As applicants explained during the telephonic discussion, applicants do not agree that the claims in question fall outside of the elected group. However, in the interest of expediting prosecution, applicants submit the present amendment drawn to methods comprising the use of a ligase-binding antibody or fragment thereof, as will be discussed in detail below. Applicants explicitly reserve the right, however, to pursue corresponding method claims comprising the use of inhibitory nucleic acids in a divisional application.

Information Disclosure Statement

Applicants acknowledge the Office's statement that the references cited in the Information Disclosure Statements have been considered. Applicants note for the record that the

Information Disclosure Statements to which the Office refers were filed on August 10, 2007 and February 22, 2008, rather than August 15, 2007 and February 22, 2008.

The Office did not consider references C105-C160 because these references have no publication date. Applicants have corrected the citations to include both the version of the GenBank accession number and the publication date of each reference. Accordingly, applicants respectfully request consideration of these references.

Specification/Informalities

The Office Action states at page 3 that "[t]he title of the invention is not descriptive" and suggests "Method for Decreasing a Protein-Protein Interaction Between an E3 Ubiquitin Ligase and an E3 Ubiquitin Ligase Substrate" as a title. Applicants respectfully disagree that the title is not descriptive. Nevertheless, in the interest of moving the present application towards allowance, applicants have amended the title as suggested by the Office.

35 U.S.C. § 112, ¶ 2

A. The Office rejected claims 41 and 45 as allegedly failing to point out and distinctly claim the subject matter. According to the Office Action at pages 3-4:

> Claim 41 (claim 45 dependent therefrom) is confusing in that, while the claim recites "an E3 ubiquitin ligase substrate", the claim does not require the presence of the E3 ubiquitin ligase [*sic*] such that a protein-protein interaction can be achieved.

Claims 41 and 45 have been canceled without prejudice or disclaimer. New independent claim 55 recites a method of decreasing a protein-protein interaction between an anergy associated E3 ubiquitin ligase and an E3 ubiquitin ligase substrate, the method comprising providing an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate. Applicants respectfully submit that this amendment obviates the present rejection and request that the rejection be reconsidered and withdrawn.

B. The Office rejected claims 41 and 45 as "indefinite in the recitation of 'anergy associated E3 ubiquitin ligase' because it is unclear as to what association the ligase must have to anergy to be encompassed within the scope of the claims" (Office Action at page 4). Claims 41 and 45 have been canceled without prejudice or disclaimer. However, claim 55 recites an anergy associated E3 ubiquitin ligase. Applicants respectfully disagree and traverse this rejection.

The specification provides a definition of "anergy associated E3 ubiquitin ligases" at page 20, line 19. Specifically, according to the specification, anergy associated E3 ubiquitin ligases are those whose expression is modulated (*e.g.*, increased or decreased) in response to calcium induced signaling. Applicants have also described seven anergy associated E3 ubiquitin ligases (*i.e.*, Itch, Cbl-b, Cbl, Cbl-3, Grail, Nedd4, and Aip4) in the specification as originally filed, *see* page 20, lines 11 and 30; and page 22, line 10. Further, nucleic acid and amino acid sequences of anergy associated E3 ubiquitin ligases are provided on page 21, lines 12-32 of the specification. Skilled practitioners, upon reading the specification, would clearly recognize the metes and bounds of the claims. Applicants therefore respectfully request that the present rejection be reconsidered and withdrawn.

35 U.S.C. § 101

The Office rejected claims 41 and 45 as being directed to non-statutory subject matter. Applicants respectfully disagree. Nevertheless, in the interest of moving the present application towards allowance, claims 41 and 45 have been canceled without prejudice or disclaimer. New independent claim 55 recites contacting the E3 ubiquitin ligase with a ligase-binding antibody or fragment thereof. Accordingly, applicants respectfully request that this rejection be reconsidered and withdrawn.

35 U.S.C. § 112, ¶ 1

A. The Office rejected claims 41 and 45 as allegedly failing to comply with the written description requirement. According to the Office Action at pages 6 and 8:

> Claim 41 is drawn to a method for decreasing protein-protein interaction between an "anergy associated" E3 ubiquitin ligase and an E3 ubiquitin

> ligase substrate by contacting an "anergy associated" E3 ubiquitin ligase with a genus of agents that decrease interaction. Claim 45 limits the ligase to Aip4 and the substrate to PKCθ. In view of a broad, but reasonable interpretation of the claims, the structure of the agent is unlimited, and encompasses, e.g., small molecule organic compounds, peptides and polypeptides, and nucleic acids. See specification at pp. 46-51.
>
> * * *
>
> Thus, because the specification fails to disclose a single representative species of such agents and it is highly unpredictable as to which agents would have such activity, the specification fails to adequately describe the genus of "agents".
>
> Given the lack of description of a representative number of "agents", the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

Applicants respectfully disagree. Nevertheless, in the interest of moving the present application towards allowance, claims 41 and 45 have been canceled without prejudice or disclaimer. New independent claim 55 has been added, which recites specific agents. That is, new claim 55 recites methods comprising contacting the E3 ubiquitin ligase with a ligase-binding antibody or fragment thereof. The specification discloses the use of ligase-binding antibodies and fragments thereof at page 48, line 34 to page 51, line 14. Skilled practitioners would thus have recognized that the full scope of the presently claimed methods was described in the specification. Accordingly, the claims are in full compliance with the written description requirement and applicants respectfully request that this rejection be reconsidered and withdrawn.

B. The Office rejected claims 41 and 45 under 35 U.S.C. § 112, ¶ 1, because according to the Office Action, the specification, "while being enabling for *in vitro* methods using an agent that degrades or denatures an E3 ubiquitin ligase, does not reasonably provide enablement for methods, including *in vivo* methods, using all "agents" as encompassed by the claims" (Office Action at pages 8 and 9). Applicants respectfully disagree. However, as discussed above, claims

41 and 45 have been canceled and new claim 55 recites specific agents, *i.e.*, a ligase-binding antibody or fragment thereof. Given the description of the targets, one of ordinary skill in the art would be able to produce suitable ligase-binding antibodies or fragments thereof without undue experimentation. Further, applicants have provided ample guidance to perform the claimed methods in cell culture, *ex vivo,* and *in vivo* throughout the specification, *e.g.*, at page 45, lines 7-26; page 47, lines 9-18; and page 48, line 34 to page 54, line 14. Accordingly, applicants respectfully request that this rejection be reconsidered and withdrawn.

35 U.S.C. § 102(b)

The Office rejected claims 41 and 45 as being anticipated by Wood *et al.* (*Mol. Cell. Neurosci.* 11:149-160, 1998; "Wood"). According to the Office Action at page 13:

> The reference of Wood teaches an Aip4 protein with an N-terminal GST fusion moiety and treating the fusion polypeptide with SDS and analyzing the protein by SDS-PAGE (p. 152, Figure 3 and p. 158, paragraph bridging columns 1-2). Because SDS is a known protein denaturant, it is considered to be an "agent" as encompassed by the claims because it would necessarily decrease protein interaction. This anticipates claims 41 and 45.

As discussed above, applicants have canceled claims 41 and 45. New claim 55 recites a method of decreasing a protein-protein interaction between an anergy associated E3 ubiquitin ligase and an E3 ubiquitin ligase substrate, the method comprising providing an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate and contacting the E3 ubiquitin ligase with a ligase-binding antibody or fragment thereof under conditions that allow the ligase to bind or ubiquitinate the E3 ubiquitin ligase substrate. Wood does not describe contacting an E3 ubiquitin ligase with a ligase-binding antibody or fragment thereof in the presence of an E3 ubiquitin ligase substrate under conditions that allow the ligase to bind or ubiquitinate the E3 ubiquitin ligase substrate, and therefore does not anticipate the presently claimed methods. Applicants therefore respectfully request that this rejection be reconsidered and withdrawn.

CONCLUSION

Applicants submit that the pending claims are allowable and request early and favorable action thereon. Applicants do not concede any positions of the Office that are not expressed above, nor do applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

The Petition for Extension of Time fee for a one-month extension ($65) is being paid on the electronic filing system by way of deposit account authorization. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 10861-0033US1.

Respectfully submitted,

Date: 11/5/09

Todd E. Garcia, Ph.D.
Reg. No. 54,112

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (877) 769-7945